

CURRENT TOPIC

Non-traumatic coma in children

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Many acutely ill children are not fully conscious. Most make a full neurological recovery as the underlying cause is treated, but considerable skill is required to distinguish the group at high risk of further deterioration, potentially leading either to death or to severe handicap. This article is an attempt to guide the worried paediatrician in casualty or on the ward faced with a child in non-traumatic coma who may need intensive care. The most effective method of deciding the order of priorities in this emergency situation is to ask oneself a series of questions.

Is the child unconscious and if so, how deeply?

This is the most important question of all and may well be the most difficult to answer. The Glasgow Coma Scale was designed to assess depth of coma after head injury in adults and has been used in paediatric non-traumatic coma.^{1–3} Although alternatives such as the Sesia scale have less interobserver variability, probably because there are fewer choices,⁴ the Glasgow scale is very familiar to nursing staff and casualty officers and works well down to the age of 5. In those below that age, the motor and eye opening scales may be used (except that children below the age of 9 months cannot localise pain), but a modification of the verbal scale is needed. The modified James scale (table 1) has been used successfully in several UK centres, can be consistently reproduced between observers,⁵ and has therefore been endorsed by the British Paediatric Neurology Association. The response to pain should be examined both with a supraocular stimulus (for

localisation, flexion, and extension) and with nailbed pressure, for example with a pencil (for withdrawal). There may be a need for flexibility in terms of the overlap between the age groups. Thus, children of any age who are restless and talking unintelligibly have a verbal score of 2 and are therefore deeply unconscious; they are at high risk of further deterioration. At initial presentation, it is preferable to err on the side of recording too low a score, as it is easier to withdraw treatment from a child who is improving than to resuscitate one who deteriorates.

Is the intracranial pressure raised?

The initial priorities are to establish an airway to ensure adequate gas exchange and to measure the mean arterial pressure (MAP), maintaining it as high as possible acutely. For an unconscious patient, the time to ask oneself whether or not there is intracranial hypertension is as soon as this basic triage is done, as irreversible brain damage may supervene long before it is possible to measure the intracranial pressure (ICP). The answer for all non-traumatic encephalopathies, whether infectious^{6–9} or not,^{9–12} is almost certainly “yes”; whatever the controversies about the benefits of monitoring, appropriate management in the acute situation prevents death and handicap.

Intracranial hypertension is thought to cause brain damage by at least two mechanisms. Firstly, reduced cerebral perfusion pressure (CPP = MAP – ICP) causes cerebral ischaemia, particularly in the borderzones between the main arterial territories; this may be associated with seizures, for example in hypertensive encephalopathy,¹³ but is often clinically silent. Secondly, if there are differences in pressure between the forebrain compartment and the posterior fossa, one (uncal herniation) or both (diencephalic and midbrain/upper pontine herniation syndromes) temporal lobes may herniate through the tentorium. Similarly, if there is a pressure differential between the posterior fossa and the spinal canal, the brain may herniate through the foramen magnum (lower pontine and medullary herniation syndromes). Brain herniation causes direct mechanical damage and also ischaemia and haemorrhage secondary to vascular distortion. Central or uncal herniation through the tentorium is compatible with intact survival; herniation through the foramen magnum is not. These syndromes, and the changes from one to the next which signify progressive herniation, are

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Table 1 Modified Glasgow coma scale

	>5 years	<5 years
<i>Eye opening</i>		
4	Spontaneous	
3	To voice	
2	To pain	
1	None	
<i>Verbal</i>		
5	Orientated	Alert, babbles, coos, words or sentences—normal
4	Confused	Less than usual ability, irritable cry
3	Inappropriate words	Cries to pain
2	Incomprehensible sounds	Moans to pain
1	No response to pain	No response to pain
<i>Motor</i>		
6	Obeys commands	Normal spontaneous movements
5	Localises to supraocular pain (>9 months)	
4	Withdraws from nailbed pressure	
3	Flexion to supraocular pain	
2	Extension to supraocular pain	
1	No response to supraocular pain	

Table 2 Brain stem examination¹²⁰

Response to pain	Flexion to supraocular pain Extension to supraocular pain None	Diencephalic Midbrain/upper pontine Lower pontine
Posture	Normal Hemiparesis Decorticate Decerebrate Flaccid	Brainstem intact Uncal herniation Diencephalic Midbrain/upper pontine Lower pontine
Tone/reflexes/plantars	Normal Unilateral pyramidal Bilateral pyramidal Flaccid/extensor plantars	Brainstem intact Uncal herniation Diencephalic Lower pontine
Oculocephalic (doll's eye) <i>Exclude cord injury</i> <i>Turn head from side to side, watch eyes</i>	Saccadic eye movements Full deviation eyes away Minimal deviation eyes No movement eyes	Normal forebrain control Diencephalic Midbrain/upper pontine Lower pontine
Oculovestibular (caloric) <i>Exclude perforated eardrum</i> <i>Head in midline and 30° back</i> <i>Inject 20 ml ice cold water into ear canal</i>	Nystagmus Full deviation eyes towards Minimal deviation eyes No movement eyes	Normal forebrain control Diencephalic Midbrain/upper pontine Lower pontine
Pupil size	Normal midpoint Small Unilaterally large Bilaterally large	Midbrain/upper pontine Diencephalic Uncal herniation Lower pontine
Pupil response to light <i>Bright torch</i>	Brisk Unresponsive	Brainstem intact Midbrain/upper pontine
Respiratory pattern	Normal Cheyne-Stokes Hyperventilation Ataxic, shallow Gasping, slow, irregular	Brainstem intact Diencephalic Midbrain/upper pontine Lower pontine Medullary

Bold refers to clinical signs of potentially reversible cerebral herniation.

recognisable clinically^{7 8} (tables 2 and 3), although appropriate clinical testing of the brain stem reflexes is often not performed routinely (table 2). Emergency management of intracranial hypertension at the time of presentation is potentially life saving in all encephalopathies. The important steps are: (i) to memorise the stages of progressive herniation which are compatible with intact survival (in **bold** in tables 2 and 3); (ii) to acquire the habit of serially examining the patient's conscious level (table 1) and brain stem reflexes (table 2) with these concepts in mind, so that progression is recognised immediately; and (iii) to learn the management algorithm so that action is taken as swiftly as possible.

The examination of the brain stem is best carried out with the possibility of uncal or central herniation in mind. It is therefore essential to examine the posture, response to pain, tone,

peripheral reflexes, and plantar response as well as the oculocephalic (doll's eye) reflexes, pupil size and response to light, and respiratory pattern (table 2). If it is not possible to perform oculocephalic testing, for example, if there is any suspicion of a cervical injury, or if there is any doubt over the findings, oculovestibular or caloric testing should be undertaken using ice cold water (table 2). The most important use of these brain stem signs is in the recognition of progressive uncal and central transtentorial herniation (table 3), so that the early stages may be recognised and appropriately managed before irreversible herniation has occurred. The signs of the diencephalic stage of central herniation may be mimicked by drugs, toxins, and metabolic abnormalities, as well as occurring intra- and post-ictally. In the acute situation, however, it is always better to assume that central herniation is imminent and take appropriate action, rather than waiting for clear evidence of progression through the stages, which may occur very rapidly. Recovery is extremely unlikely if the patient has reached the lower pontine or medullary stage, so that if children are seen with some or all of the signs, either of uncal herniation or of the diencephalic or mid-brain/upper pontine phases of central herniation, emergency management of presumed raised ICP is mandatory.

Papilloedema is very rarely seen in acute encephalopathies, even if the intracranial pressure is very high.^{8 14 15} Corneal, gag, and cough reflexes may also be elicited, but do not provide essential additional information and are therefore omitted here. If the lateral ventricles are small on the computed tomography (CT) scan in a child in coma it is likely that the ICP is raised; but such a scan is often reported as normal, and raised ICP should be assumed even if there is no evidence of brain swelling on the CT scan.^{7 16 17} Figure 1 shows CT scan abnormalities commonly seen in unconscious children.

What is the emergency management of the unconscious patient?

The potentially life saving manoeuvres required in an unconscious child who has just arrived in casualty can be considered separately from the long term management of the comatose patient, which is rather more controversial. The main priority in these extremely sick children is to maintain the airway and the systemic circulation and to correct significant metabolic derangements. Shock is a commonly associated finding, particularly when the aetiology is meningitis¹⁸; it should be treated rapidly with plasma and if necessary, inotropic support. Adrenaline is relatively contraindicated, as there is evidence for an associated lactic acidosis, at least in septic shock.¹⁹ Hypoglycaemia, which is common in association with any serious illness in the developing world,²⁰ must be treated, but salt wasting is an important association with conditions such as meningitis; initial fluid therapy should aim to slowly replace salt and water losses²¹⁻²³ as well as maintain

Table 3 Herniation syndromes

<i>Uncal</i>	Unilateral fixed dilated pupil Unilateral ptosis Minimal deviation of eyes on oculocephalic/oculovestibular testing Hemiparesis
<i>Diencephalic</i>	Small or midpoint pupils reactive to light Full deviation of eyes on oculocephalic/oculovestibular testing Flexor response to pain and/or decorticate posturing Hypertonia and/or hyperreflexia with extensor plantars Cheyne-Stokes respiration
<i>Midbrain/upper pontine</i>	Midpoint pupils, fixed to light Minimal deviation of eyes on oculocephalic/oculovestibular testing Extensor response to pain and/or decerebrate posturing Hyperventilation
<i>Lower pontine</i>	Midpoint pupils, fixed to light No response on oculocephalic/oculovestibular testing No response to pain or flexion of legs only Flaccidity with extensor plantars Shallow or ataxic respiration
<i>Medullary</i>	Pupils dilated and fixed to light Slow, irregular, or gasping respiration Respiratory arrest with adequate cardiac output

Bold refers to clinical signs of potentially reversible cerebral herniation.

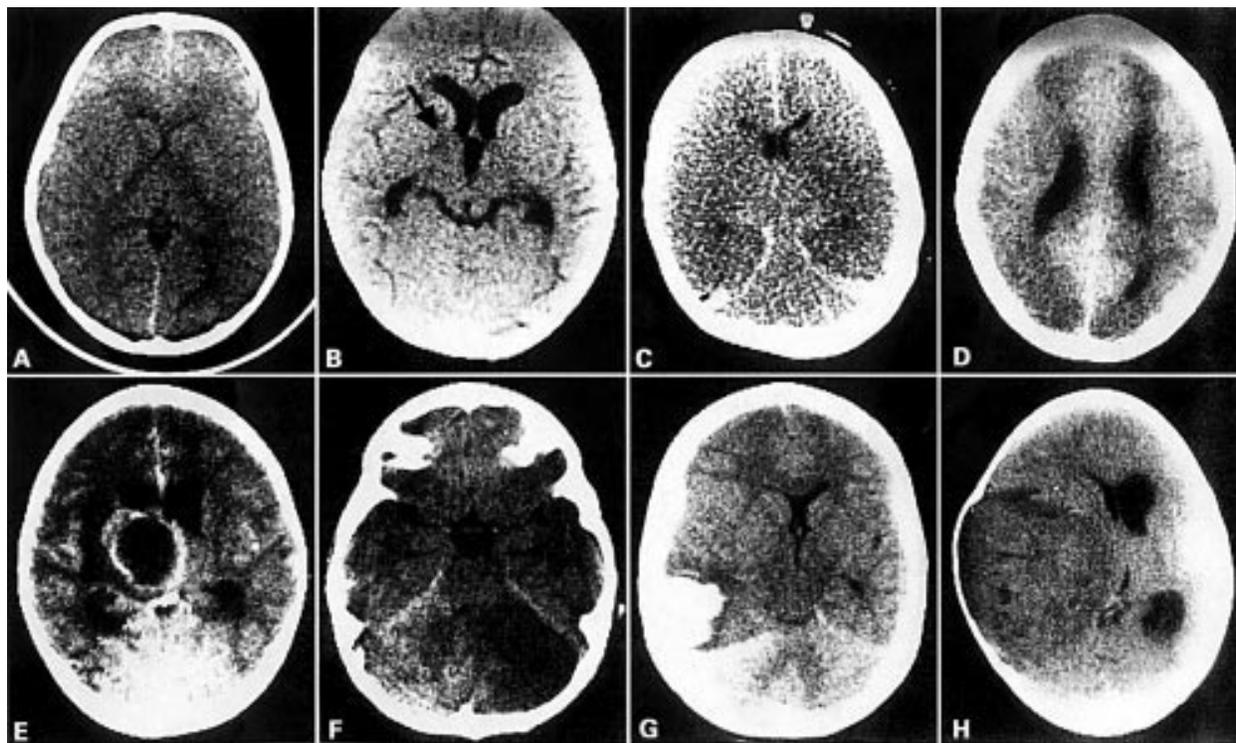


Figure 1 CT scan abnormalities commonly seen in unconscious children (A) Small ventricles suggestive of acute brain swelling in a patient in acute coma. (B) Acute hydrocephalus in a patient with a reduced level of consciousness after status epilepticus. There is a small infarct in the basal ganglia on the left, indicated by the arrow. CSF showed a pleiocytosis and acid fast bacilli; the child responded to antituberculous therapy. (C) Low density in the cerebral hemispheres compared with the posterior fossa, suggestive of widespread ischaemia. There is high density in the falx suggestive of blood and it is likely that this child has been shaken. (D) Bilateral anterior and posterior watershed infarcts in a child with hypertensive encephalopathy in whom blood pressure had been reduced precipitously. (E) Contrast enhanced CT scan showing a cerebral abscess in a child with a hemiparesis, a reduced level of consciousness, and a fever. (F) Low density in the right cerebellum compatible with an infarct in a child with an acute vertebrobasilar dissection. (G) CT scan without contrast showing a left sided intracerebral haematoma in a child with an arteriovenous malformation. (H) Large supratentorial tumour and acute hydrocephalus.

adequate nutrition. Resuscitation and maintenance of systemic homeostasis are the priorities in the acute situation and there is no case for fluid restriction; however hypo-osmolar fluids such as 5 or 10% dextrose are contraindicated because of the risk of delayed cerebral oedema.

In a drowsy child (Glasgow coma score 12 or more), with an adequate airway, a well maintained blood pressure and no signs of brain stem compromise, a single dose of 0.25–0.5 g/kg 20% mannitol is often associated with rapid improvement in conscious level. Although not contraindicated,²⁴ if the aetiology is intracranial haemorrhage, there is a risk that as the brain oedema is reduced, the rate of

bleeding will increase; an emergency CT scan is therefore mandatory if the patient does not regain full consciousness immediately after the dose has been given. If the level of consciousness is deteriorating or there is evidence of reversible brain stem compromise (signs in **bold** in tables 2 and 3), the child must be immediately ventilated. This has at least two beneficial effects: firstly, the airway is protected, making respiratory arrest less likely; and secondly, ICP will decrease because cerebral blood flow and therefore blood volume are directly related to pCO_2 .²⁵ Clinical experience suggests that mannitol may also help in this situation, at least in the short term, although there is little evidence available.^{8 24 26 27} Mannitol should not be administered in renal failure

Table 4 Emergency management of the unconscious patient

Establish airway and give high flow oxygen by mask
Measure blood pressure and resuscitate with salt containing fluids/inotropes if low; do <i>not</i> reduce immediately if high
Perform Dextrostix testing and simultaneous true blood sugar and give dextrose if low
Assess level of consciousness using the modified Glasgow coma scale (table 1)
Assess brain stem function (table 2) and decide whether the patient has evidence of central or uncal herniation (table 3)
Lift the eyelids and look for tonic deviation of the eyes or nystagmus
Examine the fundi for papilloedema (rarely seen in acute encephalopathy; absence does not exclude intracranial hypertension), retinal haemorrhages, and macular star suggestive of hypertension
If modified Glasgow coma score is less than 12 or there is evidence of herniation, intubate and ventilate
If modified Glasgow coma score is between 12 and 14, or intubation is not possible immediately and there is evidence of progressive uncal or central herniation (table 3), give mannitol 0.25 g/kg
If there is tonic deviation of the eyes or nystagmus, assume subtle status epilepticus and give a benzodiazepine and/or phenytoin
If the child is febrile and is either under the age of 12 months or is older than 12 months and has a Glasgow coma score greater than 12, undertake a lumbar puncture (table 5) after checking that the child is not in subtle status. The CSF pressure should be measured with a transducer or a manometer. A dose of mannitol 0.25 g/kg should be given if the pressure is greater than 15 cm H ₂ O or if there is evidence of deterioration in the modified Glasgow coma score or the brain stem signs after the lumbar puncture. If the CSF is cloudy, dexamethasone may be given before starting a third generation cephalosporin
If the child is afebrile or febrile with a deteriorating level of consciousness, do not perform lumbar puncture, but start a third generation cephalosporin and aciclovir and ring the nearest paediatric intensive care unit with access to a neurosurgical unit to request transfer by their transport team for CT scan and further management

as it is excreted by the kidneys and makes dialysis difficult.

Clinical seizures should be treated immediately, as they are usually accompanied by an increase in ICP,²⁸ may precipitate with cerebral herniation,²⁹ and may be associated with excitotoxic³⁰ and ischaemic³¹ mechanisms of secondary brain damage. Generalised tonic-clonic seizures occur, but subtle seizures, including unilateral clonus, eye deviation, nystagmus, and eyelid twitching are characteristic of prolonged status epilepticus, which is common in non-traumatic coma,^{31, 32} but often remains undetected, particularly in ventilated patients. Lifting up the eyelids to look for tonic deviation of the eyes or nystagmus is therefore worthwhile. It is sensible to control fever, as high body temperature tends to lower the seizure threshold. The standard protocol for the management of status epilepticus may be followed.³³ A benzodiazepine should be used initially, but it is essential to have access to a ventilator if more than one bolus dose is required in an unconscious patient. There are few data on the pharmacokinetics and efficacy of rectal paraldehyde (0.4 ml/kg mixed with an equal volume of olive oil), but it is cheap, is often associated with the cessation of seizures, and is said to have less effect on respiratory drive than either benzodiazepines or barbiturates. Intravenous phenytoin (18 mg/kg) may be given over 20 minutes with ECG monitoring. Intramuscular phenobarbitone is commonly used in the developing world, but one study showed that a dose of 10 mg/kg was often ineffective³⁴, a recent controlled trial showed that mortality was higher in unventilated patients with cerebral malaria treated with the usually effective dose of 20 mg/kg,³³⁻³⁵ probably because of associated respiratory depression.³⁵ This drug cannot therefore be recommended unless ventilation is feasible.

Table 4 summarises the emergency management of the unconscious patient.

What is the cause and which possible underlying causes should be treated immediately?

The cause may be apparently obvious in, for example, a child who has just been resuscitated after a cardiac arrest, a known diabetic presenting in coma, a hypertensive patient with a macular star, or a patient with severe viral hepatitis. In diabetic coma, if serum sodium does not increase in parallel with the reduction in plasma glucose, there is a serious risk of cerebral oedema and herniation³⁶; this is the commonest cause of death in diabetic children.³⁷ This is probably preventable if fluid losses are replaced over a 48 hour period with at least 125 mmol of sodium per litre over the first 24 hours.^{38, 39} The prognosis for hypertensive encephalopathy is excellent if an ischaemic insult is not superimposed,⁴⁰ so if blood pressure is raised in an unconscious patient, it should be reduced extremely slowly. Hepatic transplantation is life saving in fulminant liver failure with progressive deterioration in conscious level,⁴¹ but the prognosis is better in

those who do not have cerebral oedema on CT scan⁴² or require ventilation.

The previously well child presenting in coma can prove more difficult diagnostically. Routine haematology, biochemistry, and microbiology may be helpful, and specific tests, including blood ammonia, lactate, and urine toxicology screen should also be performed (table 5). Reye's syndrome¹⁴ has become very rare nowadays, probably in association with the warnings not to give aspirin to children under 12, but ornithine carbamoyl transferase deficiency still presents, often with unilateral cerebral oedema in a manifesting heterozygote.⁴³ Occasionally, other metabolic conditions may present as coma in a previously well child and accidental or deliberate poisoning is a possibility; plasma and urine should therefore be saved at the time of the acute presentation in case later investigation is required. Careful examination of thick and thin blood films for *Plasmodium falciparum* is essential in children who live in or have travelled from endemic areas, but negative studies do not exclude the diagnosis; either quinine or arthemether must be given if there is any doubt.⁴⁴

If the child is deeply unconscious, afebrile, or has focal signs, the top diagnostic priority is a CT scan rather than a lumbar puncture, as likely diagnoses include intracerebral haemorrhage, ischaemic stroke, hydrocephalus, and brain tumour. As this will inevitably mean some delay, a third generation cephalosporin and aciclovir must be given to cover the possibility of infection. There is a good case for immediate ventilation and transfer of the afebrile comatose child to a paediatric intensive care unit with access to neurosurgery; if there is a space occupying lesion and/or acute hydrocephalus, timely decompression may prevent brain herniation. In addition, if the CT scan is normal, magnetic resonance imaging may be warranted, as the posterior fossa is better shown (for example, for the diagnosis of cerebellar inflammation,⁴⁵ tumour, or ischaemia which may cause life threatening acute hydrocephalus). In addition, evidence of focal pathology may suggest ischaemic stroke or an alternative aetiology (for example, frontotemporal pathology in herpes simplex encephalitis,⁴⁶ or thalamic involvement in Japanese B⁴⁷ or Epstein-Barr⁴⁸ encephalitis). There may be a case for additional sequences, for example, fluid attenuated inversion recovery,^{49, 50} diffusion weighted imaging, magnetic resonance angiography or venography. It is important to remember that children who have been non-accidentally injured may present in unexplained coma with or without seizures.⁵¹ Careful examination of the fundi for retinal haemorrhages is mandatory and it is important to remember that cranial ultrasound does not exclude subdural haemorrhage or effusion, so that CT or magnetic resonance imaging is an essential investigation, even in those with an open fontanelle; magnetic resonance imaging is particularly useful in dating the injury and therefore deciding whether the child has been serially abused.

Table 5 Investigation of non-traumatic coma

Investigations	Indication/clinical clues	Possible abnormality	Further investigation if abnormal	Possible diagnoses	Action
Dextrostix Blood glucose	All	Low	Blood glucose Liver function tests Blood ammonia Blood lactate Blood and urine amino acids Urine organic acids	Hypoglycaemia secondary to: ● Fasting ● Severe illness ● Reye's syndrome ● Organic aciduria ● Fatty acid oxidation defect ● Haemorrhagic shock and encephalopathy Diabetic ketoacidosis	Intravenous dextrose Fluids/insulin
Blood sodium	Previous polydipsia/polyuria All	High Low High High	Urinary sodium	Hypo/hyponatraemia +/- dehydration	Appropriate fluids
Blood urea	All	High	Blood creatinine Blood film	Dehydration Haemolytic-uraemic syndrome	Rehydrate Dialysis, plasmapheresis
Aspartate transaminase	All	High	Blood ammonia	Reye's syndrome Hypoxic-ischaemic	
Blood ammonia	All (unless cause known)	High	Blood orotic acid Urine organic acids	Urea cycle defect Organic acidemia	Sodium benzoate
Full blood count and film	All	Low Hb High WBC Low platelets Sickle cells Burr cells	Hb electrophoresis	Anaemia Infection DIC, infection Sickle cell disease Haemolytic-uraemic syndrome	Transfusion 3rd generation cephalosporin Dialysis, plasmapheresis Quinine
	Residence in endemic area	Parasites on thick/thin films		Malaria	
Blood culture	Pica	Basophilic stippling	Wrist x ray—lead line	Lead encephalopathy	Chelation Appropriate antibiotics
Stool culture	All	Shigella, enteroviruses			
Mycoplasma IgG, IgM	All (unless cause known)		Chest x ray	Mycoplasma encephalitis	Erythromycin, ?prednisolone
Viral titres	Analyse if unexplained		Repeat at discharge		
Urine for toxin screen	Analyse if unexplained		Blood film—basophilic stippling, wrist x ray—lead line	Poisoning	Antidote
Blood lead	Analyse if unexplained				Chelation
CT scan without contrast	All (after resuscitation, afebrile patients should ideally be transferred for CT scan to a unit with neurosurgical facilities)	Blood ● Subdural ● Extradural ● Intracerebral Space occupying lesion Hydrocephalus ● Obstructive ● Communicating Abscess Swelling Focal low density Abnormal basal ganglia	Skull x ray/skeletal survey/clotting screen Plasma/CSF lactate, blood gas	Non-accidental injury ?Space occupying lesion ?Meningitis, especially tuberculous Cerebral abscess, herpes simplex, stroke, ADEM Leigh's syndrome, hypoxic-ischaemic, striatal necrosis	Neurosurgical referral Child protection Neurosurgical referral Antituberculous cover Neurosurgical referral Neurosurgical referral Anaerobic cover Mannitol 0.25 g/kg
Lumbar puncture	In febrile if no clinical or radiological evidence of raised ICP (delay and treat if doubt)				
● Pressure measurement ● Microscopy		High High WCC	CT scan	Meningitis/encephalitis	Mannitol, ventilate 3rd generation cephalosporin, aciclovir
● Gram, bacterial culture		High RBC	CT scan (traumatic tap should clear by 3rd bottle)	Haemorrhage/encephalitis/ non-accidental injury } Tuberculous meningitis	Neurosurgical referral, aciclovir, child protection Immediate and prolonged antituberculous therapy
● Glucose ● Protein ● PCR for viruses, TB ● Prolonged search for acid fast bacilli, culture for TB on Lowenstein-Jensen	Prodrome > 7 days, optic atrophy, focal signs, abnormal movements, CSF polymorphs < 50%, hydrocephalus and/or basal enhancement on contrast CT	Low High		Tuberculous meningitis	Immediate and prolonged antituberculous therapy
● Antibodies e.g. herpes simplex, Mycoplasma ● Lactate	Abnormal breathing/eye movements, basal ganglia lucencies		Muscle biopsy	Encephalitis Leigh's syndrome	Aciclovir, erythromycin
EEG	All, especially if ventilated or evidence of subtle seizures (nystagmus, tonic deviation of eyes, clonic jerking limbs)	Epileptiform discharges Asymmetrical foci of spikes or periodic lateralising epileptiform discharges on slow background		Status epilepticus Herpes simplex encephalitis (many patients do not have characteristic EEG)	IV benzodiazepines, phenytoin, thipentone High dose IV aciclovir for 2 weeks
MRI	Unexplained encephalopathy	Frontotemporal abnormality Thalamic abnormality	CSF for herpes simplex PCR CSF for Epstein-Barr virus (arboviruses in endemic area)	Herpes simplex encephalitis	High dose IV aciclovir for 2 weeks

If the child is febrile, CSF should be obtained once the level of consciousness is starting to improve after resuscitation. This is crucial in the developing world where children commonly have both malaria parasitaemia and meningitis,⁵² and it is not possible to distinguish between them clinically⁵³; infants, in whom cerebral herniation is exceptional because of the open fontanelle, very commonly have both.⁵² In the developed world, there is also a risk of suboptimal management if CSF is not obtained⁵⁴; this may become increasingly important as antibiotic resistance increases.⁵⁵ Although there is a risk of cerebral herniation,^{7, 29} a normal CT scan does not exclude intracranial hypertension⁷ and may not be essential if there are no focal signs.⁵⁶ Diagnosis and treatment of subtle seizures is essential prior to lumbar puncture,²⁹ however, and the procedure must be postponed in children over 12 months who have a Glasgow coma score less than 12 (table 1) or signs of herniation (table 3). The pressure should be measured with a transducer (a device designed to measure blood pressure may be used) rather than by displacement into manometer tubing. Ideally, if the child is not fully conscious, he or she should be in the intensive care unit and ventilated during the lumbar puncture; if this is not possible, a dose of mannitol should be available, to be given if the pressure is high.

For measurement of cerebral perfusion pressure (CPP), it is important that CSF pressure is measured in mm Hg (if obtained in cm H₂O, the pressure should be divided by 1.35). The CSF should be sent for a cell count, protein, glucose, and a Gram stain. If there are white cells but no organisms on the Gram stain, a careful search for acid fast bacilli after Ziehl–Nielsen staining should be performed and the CSF should be put up for culture for *Mycobacterium tuberculosis*. This is particularly important if there are clinical or radiological features, specifically hydrocephalus or ventricular enhancement, suggestive of tuberculous meningitis.^{57, 58} Viral antibodies should also be requested, particularly looking for herpes simplex. The polymerase chain reaction (PCR) may be used to suggest the diagnosis in tuberculous meningitis, enteroviral, or herpes simplex⁵⁹ infection, but it is technically difficult to avoid contamination. PCR is also available for other organisms, including meningococcus and pneumococcus, and may be useful in confirming the diagnosis in partially treated infections, provided that the limitations of sensitivity and specificity are taken into account. It is essential to liaise closely with the local microbiology laboratory, as the range of likely diagnoses varies considerably with location.^{60–63}

There is no doubt that a seriously ill child in non-traumatic coma should be covered with a broad spectrum antibiotic which is also appropriate to treat meningitis, should this prove to be the underlying cause. Recent studies have suggested that the third generation cephalosporins, cefotaxime, ceftazidime, and ceftriaxone used alone give good antibiotic cover for meningitis, but the combination of chloramphenicol and penicillin is still used in the

developing world. The emergence of resistant organisms means that microbiological advice should always be sought, particularly if the patient is in a high risk group, for example, a child with sickle cell disease or splenectomy on prophylactic penicillin. There is some evidence that dexamethasone, given before the antibiotic, reduces the incidence of deafness and possibly neurological handicap,⁶⁴ although the data were collected when *Haemophilus influenzae* was a common pathogen, and the benefit is less certain for pneumococcal or tuberculous meningitis.^{65–67} A child presenting with acute seizures should be treated with aciclovir to cover the possibility of herpes simplex encephalitis and if the diagnosis is likely, this drug should be continued at high dose for two weeks because of the risk of relapse.⁶⁸ If there is any suspicion of tuberculous meningitis, for example, if there is hydrocephalus on the CT scan or the CSF sugar is low, treatment with antitubercular therapy should be considered. The treatment of other possible infections such as *Mycoplasma pneumoniae* remains controversial, but most physicians use erythromycin in idiopathic coma until the results of antibody testing are known.⁶⁹

There is little evidence that specific management improves outcome in ischaemic encephalopathy,⁷⁰ but carbon monoxide poisoning should be treated with hyperbaric oxygen.⁷¹

What is the management if the child remains unconscious?

MONITORING OF INTRACRANIAL PRESSURE

After admission to intensive care locally or transfer to the regional centre, the next few hours are usually spent in establishing the cause of coma and improving the child's general condition. If the child remains unconscious for more than six hours and the blood pressure can be maintained, ICP monitoring should be considered. If there is irreversible brain stem damage clinically, or an electroencephalogram (EEG) predictive of very poor outcome, ICP monitoring is unlikely to be of benefit. Great care should be taken if there is a bleeding diathesis. Extradural ICP monitoring has been undertaken safely in patients with liver disease with a prolonged prothrombin time, but a platelet count of below $50 \times 10^9/l$ is an absolute contraindication. Bleeding may be more likely in patients with meningitis in whom the vessels may be inflamed. Although various techniques for monitoring ICP have been described, the Camino system, which has a fiberoptic sensor, and may be placed subdurally, intracerebrally, or intraventricularly is used very widely now. The catheters are expensive but the technique appears to be very safe, can be performed at the bedside, and gives reliable measurements over several days, even at high ICP.

MAINTENANCE OF AN ADEQUATE CEREBRAL PERFUSION PRESSURE

The baseline ICP may be normal or high and in addition there are often plateaus or spikes of very much higher ICP which are probably secondary to autoregulatory vasodilatation. There

is evidence that in non-traumatic coma, outcome is related more to minimum CPP than to maximum ICP,^{9,72} although there is controversy over the ideal CPP to aim for, which may depend on the age of the child. In adults with head injury there is some evidence that the cerebral circulation is unstable at a CPP of less than 70 mm Hg and that outcome is poor for patients whose CPP cannot be maintained at or above this level.⁷³ The small amount of data available in non-traumatic coma in children suggests that outcome is poor if mean CPP is consistently lower than 65–70 mm Hg,^{9,74} but there may be a number of confounding factors, including CO₂ tension; current advice is to maintain CPP above a minimum of 50 mm Hg. The main priority is to maintain the systemic circulation, with plasma if the circulation is underfilled, and otherwise with inotropic support. There is some evidence that maintenance of the systemic circulation in this way may prevent ICP spikes.

MANAGEMENT OF PERSISTENT INTRACRANIAL HYPERTENSION

Management of the intracranial hypertension is rather more controversial. A mass may require surgical management and acute hydrocephalus may need emergency drainage. The child should be nursed flat with the head in the midline, so that venous drainage from the head is not obstructed, and with the head either flat or tilted up to 30°. The patient should be handled as little as possible and nursing procedures such as suction should be performed with great caution. There is considerable controversy over the use of hyperventilation in unconscious patients. There is no evidence that prophylactic hyperventilation prevents intracranial hypertension, and there is evidence that it is possible to reduce cerebral blood flow below the ischaemic threshold in unconscious patients.⁷⁵ The current recommendation is to ventilate to normocapnia; the patient can then be hyperventilated or bagged during ICP spikes. It is essential to wean patients from the ventilator slowly.

Fluid management can be very difficult and should be tailored for the individual patient's needs. There is considerable controversy over fluid restriction, which has been shown to be potentially harmful in patients with subarachnoid haemorrhage and meningitis.^{21–23} The syndrome of inappropriate secretion of ADH, for which fluid restriction is indicated, is relatively rare; instead cranial diabetes insipidus may require careful management.⁷⁶ It is essential that the systemic circulation is well filled and that large volumes of hypo-osmolar fluids are not given. To manage these patients properly it is essential to monitor blood pressure, central venous pressure, urine output, weight, core and peripheral temperature, plasma and urine electrolytes, and osmolality at least six hourly and to make appropriate management decisions with the same frequency. Mannitol may reduce spikes of ICP very rapidly and acts either as an osmotic diuretic or by reducing cerebral blood volume. As with

hyperventilation, there is no evidence that regular prophylactic mannitol is of benefit.

A few years ago there was a vogue for using anaesthetic agents which reduce ICP by reducing cerebral metabolic demand and therefore cerebral blood flow and blood volume. There is no evidence that barbiturates and other sedatives are of any benefit in global cerebral ischaemia. Although there may be an intermediate group of patients in coma from other causes who might benefit from barbiturate therapy, the risk of hypotension probably outweighs any useful effect in reducing ICP. In addition, drug levels may remain high several days after the drug has been discontinued, making the diagnosis of brain death impossible. Reducing the body temperature by 1°C can reduce cerebral metabolic rate considerably and there is evidence for an additional beneficial effect on ischaemic brain tissue. Those units using profound hypothermia have abandoned this management strategy because of neutropenia and infection,⁷⁷ but recent evidence suggests a benefit for mild hypothermia in head injury⁷⁸ (although a controlled trial in adults was negative), stroke, and neonatal hypoxic-ischaemic encephalopathy. There is, therefore, a case for maintaining normothermia or mild hypothermia in unconscious patients, although research is needed as fever may have an important antiparasitic effect in infectious encephalopathies. One major advantage is that hypothermia is easily reversible.

As some of the pharmacological interventions discussed above may be definitely harmful, it is often worth considering simple mechanical manoeuvres such as CSF drainage if intracranial hypertension persists.⁷⁹ An intraventricular cannula may be placed, although this is difficult if the ventricles cannot be seen on CT scan. If it is impossible to maintain an adequate cerebral perfusion pressure in a child with a treatable cause for coma in whom neurophysiology is preserved, it may well be worth considering surgical decompression.^{80–82}

MONITORING OF ELECTROENCEPHALOGRAPHIC SEIZURE ACTIVITY

Once an unconscious patient is ventilated, it is usually impossible to detect clinical evidence of seizures, but a substantial proportion have ongoing status epilepticus.⁸³ A 1–4 channel cerebral function monitor can be used to detect the majority of electrical discharges,^{84,85} but requires considerable neurophysiological backup, including regular full 16-channel EEG,⁸⁶ so that the data are interpreted correctly and focal discharges are not missed. The pathophysiology of epilepsy occurring in the context of coma is poorly understood. There are a number of reasons for seizures to occur, for example, fever, ischaemia in the anterior and posterior cortical borderzones, release of excitotoxic neurotransmitters after ischaemia, particularly in the hippocampal region of the temporal lobe, direct cortical invasion and thrombophlebitis in meningitis, small vessel vasculitis in conditions such as haemolytic-uraemic syndrome, vasospasm, stenosis or

occlusion of the basal cerebral vessels in meningitis, and perhaps venous thrombosis in conditions such as cerebral malaria where the venous system is the site of parasitic invasion. One benefit of neurophysiological monitoring is to give early warning of potentially treatable complications, presenting either as deterioration in the background pattern or as seizure discharges.

It has been argued that prolonged seizures and status epilepticus in unconscious patients simply reflect the degree of brain damage already sustained, but there is evidence that poor outcome is associated with the presence of prolonged seizures in a number of encephalopathies.⁸⁷⁻⁹² In a study using CFAM monitoring, outcome (but not mortality) was related to number and duration of electroencephalographic seizures and to the duration of the longest seizure.⁹² There is therefore an argument for monitoring and aggressive management, but there have been no studies looking at the effect of treatment of subclinical seizure discharges on outcome. More research is needed in this area.

Are there any other potentially treatable secondary phenomena causing neuronal damage?

There is a large amount of experimental data available suggesting a role for substances such as free radicals, excitotoxins, and calcium, released during a cascade of biochemical reactions after ischaemia, in the causation of brain damage. In some patients, for example, those with meningitis, there is evidence for an inflammatory vasculopathy, with spasm, stenosis, and occlusion of the large (and perhaps the small) cerebral vessels.⁹³ Anticoagulation has been suggested, but these patients commonly have a bleeding diathesis and there have been no randomised studies to date, so this treatment cannot be recommended.⁹⁴ It is possible that the next few years will bring appropriate drugs to antagonise these phenomena but none is available as yet.

What is the prognosis?

This becomes the most important question in the minds of parents and professionals. There is no doubt that prolonged coma after a hypoxic-ischaemic insult in childhood carries a very poor prognosis,⁷⁰⁻⁹⁵ but most children surviving infectious encephalopathies have a good outcome,⁸⁹⁻⁹⁶⁻⁹⁷ with mild or moderate difficulties only, which are often subtle.⁹⁶⁻⁹⁷ If global ischaemia has not occurred during the course of other encephalopathies, the prognosis may well be very much better than is obvious in the first few weeks after the child comes off the ventilator.⁹⁹⁻⁹⁹ Cortical blindness often recovers.¹⁰⁰ A child with either a hemiparesis or a mild extrapyramidal disorder, such as chorea, in the first few weeks after coma, may well improve considerably, although those left with a dystonic¹⁰¹ or spastic quadriplegia are less likely to do well. Later onset movement disorders are often difficult to treat, although some respond to drugs.¹⁰²⁻¹⁰³ Cognitive function may recover sufficiently for children to return to

their former schools, but concentration may be poor, processing speed is often reduced, and there may be subtle disorders of executive function, all of which may make learning new material difficult. Behavioural difficulties are very common and may be very difficult for families to deal with in the context of their child's life threatening illness.

The prediction of outcome in the acute stages requires considerable experience but is not shirked by good teams. It is obviously important to discuss the prognosis with the parents, but although it is essential to spell out the truth as clearly as possible, it can be as important not to be too gloomy, unless a poor outcome is beyond reasonable doubt, as most families fear the worst instinctively. Aetiology, depth, and duration of coma have all been shown to be associated with outcome in large series,^{1-3 87-92 104-106} but have relatively limited utility for the individual patient, either because discrimination between good and poor is not good enough or because by the time the picture is clear, withdrawal of life support is no longer an option. Serial EEGs can be very helpful in giving an early idea of prognosis when the patient is still on intensive care,^{86 107} especially when they are combined with multimodal evoked potentials.¹⁰⁷ Neuroimaging may also be useful; poor outcome is usual if there is widespread low density, suggesting global ischaemia.¹⁰⁸ It is, however, important to realise that recovery of consciousness is expected if the lesion (however large) is focal, and in many of these cases, the residual handicap is mild.¹⁰⁹ Brain death may be diagnosed clinically in the majority of patients, although training is required,¹¹⁰ and in certain patients (for example, infants and those with uncertain aetiology), confirmatory tests are useful.¹¹¹ On transcranial Doppler ultrasound, a direction of flow index below 0.8 for more than two hours is very suggestive of irreversible brain stem death.¹¹²⁻¹¹³

What happens next?

Early rehabilitation, by a team comprising doctors, nurses, teachers, a physiotherapist, occupational and speech therapists, and a psychologist, is often very rewarding after childhood non-traumatic coma.¹¹⁴ Reintegration into school often requires time, with considerable input from team members. It is essential to test hearing early,¹¹⁵⁻¹¹⁶ particularly after meningitis, and to provide appropriate aids if necessary, although long term follow up is also required, as some patients change over time.¹¹⁷ Many children who have had seizures acutely do not develop epilepsy at follow up, and may be weaned from their anticonvulsants after three to six months. Patients who do develop epilepsy require close supervision of their anticonvulsant drugs, as control can make a considerable difference to cognitive and behavioural outcome. Epilepsy surgery may be very successful if there is a unilateral temporal focus.¹¹⁸⁻¹¹⁹

Even if to the physician, the child has a relatively good outcome, for the family, subtle changes in personality or social perception

have often changed their much loved “normal” child into somebody with long standing problems. This is usually utterly devastating and families need considerable long term support from team members and from the appropriate parent support groups. Much more support will be required for those with severe handicap and for the relatively small group of children left in a vegetative state,³⁸ as the burden of caring often overwhelms parents and siblings. There is a need for more research so that outcome, rather than survival, can be improved for this important group of children.

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